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A Novel and Convenient Approach to Functionalized 2,6,9-Trioxa-bicyclo[3.3.1]nona-3,7-dienes (Bridged Bis-Dioxines).

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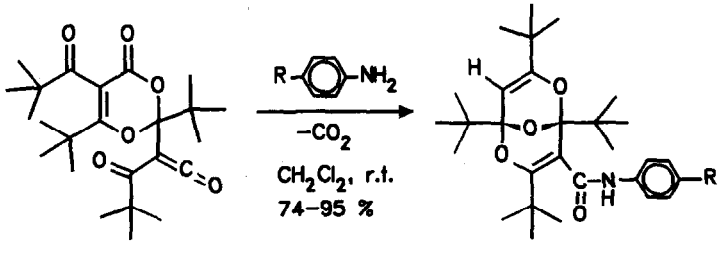
Abstract: The synthesis of N-aryl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4-carboxamides **2** by reaction of dipivaloylketene-dimer **1** with aromatic amines is described. Bis-derivatives **5**, **6** resp. are formed from **1** and aromatic diamines. The structure of N-phenylcarboxamide **2a** was proved by X-ray crystallography, the chirality of these compounds (e.g. **2b**) established by NMR studies. A reasonable reaction pathway for the unusual transformation **1** → **2** is discussed, too.

α-Oxoketenes are highly reactive molecules and cannot normally be isolated or observed under ordinary reaction conditions. These ketenes, however, can be stabilized by sterically protecting substituents such as *tert*-butyl groups. Recently, we have described the synthesis of dipivaloylketene and its subsequent [2+4] cyclodimerization to **1**.[1] This highly hindered ketene, although still an α-oxoketene, is extremely stable and is not attacked by oxygen or moisture.[1] We are currently exploring the chemistry of this intriguing molecule (**1**) in our laboratories. Here we report a new and efficient approach to 2,6,9-trioxabicyclo[3.3.1]nona-3,7-dienes **2** from reaction of **1** with aromatic amines.

The reaction of dipivaloylketene-dimer **1** with *p*-substituted aromatic amines (1.05 equiv.) was carried out in CH_2Cl_2 solution at room temperature. The progress of the reaction was followed by thin layer chromatography which revealed a very pronounced substituent effect on the overall reaction time (1-24 h; see Table 1). After removal of the solvent, the products **2a-d** were digested with cold MeCN and thereby obtained in good to excellent yield and high purity.



1 **2**

Table 1

2	R	reaction time (h)	mp. (°C)
a	H	24	120-122
b	OMe	6	166-167
c	NMe_2	2	166-168
d	NH_2	1	190-192

Scheme 1

Structure elucidation of these products was initially based on microanalytical data which indicated that, apart from the addition of the amine, one equivalent of CO_2 had been lost. The IR spectra showed – in sharp contrast to **1** – only one absorption in the carbonyl region (1660 cm^{-1}) assigned to a carboxylic amide. Moreover, the ^{13}C-NMR spectrum featured no signals downfield from 167 ppm, demonstrating the absence of any *tert*-butylcarbonyl group in the molecule. The ^1H-NMR spectra exhibited a sharp singlet between 4.85 and 4.90 ppm. From these spectroscopic data[2] it became evident that an unusual rearrangement must have taken place during that reaction. The ensemble of data was best reconciled with the bicyclic system **2**, however, final confirmation of the structure proposed was obtained from an X-ray crystallographic analysis of **2a** (Figure 1).[3]

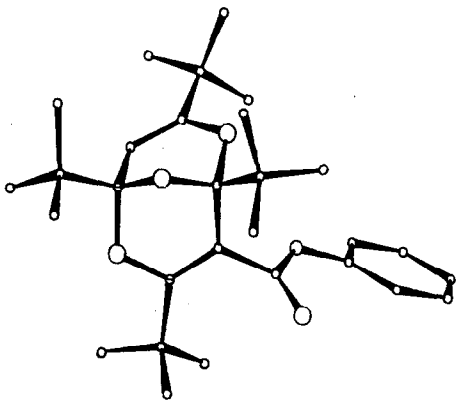
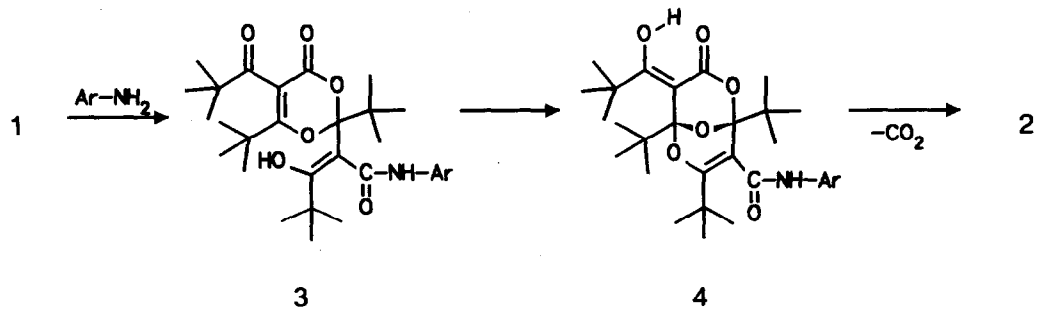


Figure 1: The molecular structure of **2a**.

The heterocyclic system identified in the present study is rather uncommon. There are only two other compounds reported, possessing the 2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene ring system, namely the 1,3,5,7-tetramethyl derivative (obtained from acetylacetone *via* organometallic intermediates),[4] and the 4,8-dicarbaldehyde (a selfcondensation product of triformylmethane).[5] These are both dissymmetric molecules having a 2-fold rotational axis as the only element of symmetry, and therefore exhibit axial chirality.[4d,5a]

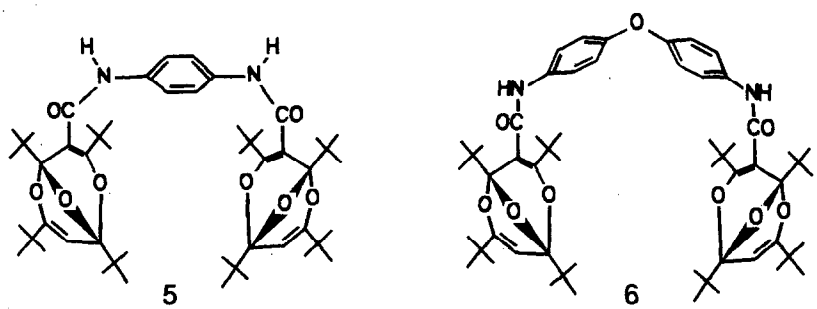
In contrast, **2a-d** are the first unsymmetrical functionalized derivatives of this bridged bicyclic system. The chirality of these compounds was established by ^1H-NMR studies using chiral shift reagents. When $Eu(hfc)_3$ was employed as reagent, a nice splitting (ratio 1:1) of all the signals in the proton NMR spectrum (200 MHz, $CDCl_3$) of e.g. **2b** was observed (e.g.: δ (H-8) = 4.87 ppm; with $Eu(hfc)_3$ δ = 5.23 and 5.28 ppm).

A possible reaction mechanism for the formation of **2** is outlined in Scheme 2. In the first step, the aromatic amine attacks the ketene functionality in α-oxoketene **1** to furnish a ß-ketoamide. Most likely it is this nucleophilic addition to the ketene, that is highly accelerated by donor-substituents (cf. Table 1). The enol-form of this ß-ketoamide (**3**) now undergoes an intramolecular Michael-type addition to give trioxabicycle **4**. Elimination of CO_2 from **4** leads to the final product **2**.



Scheme 2

From the above, one might expect that other amines (or nucleophiles in general) react in a similar way. So far, we were able to extend this reaction to aromatic diamines. Thus, when **2d** (cf. Table 1) was treated with a second equivalent of ketene **1** the corresponding 1,4-bis-substituted p-phenylendiamine **5** (mp. 270-272 °C) was obtained. In a similar experiment 4,4'-diamino-diphenyl ether was treated with 2 equivalents of **1** in MeCN solution. After two days at room temperature, the precipitated product **6** (mp. 208-211 °C) was collected in 93% yield.[6] These "crab"-like molecules are of particular interest, due to the known good coordinating ability of the trioxabicyclodiene moiety to transition metals.[4]



However, when aliphatic amines (e.g. diethylamine or benzylamine) were employed in this reaction, the only isolable products were N-substituted dipivaloylacetamides,[7] produced by addition of the amine to the ketene functionality in **1** and concomitant degradation of the dioxinone ring by a second equivalent of amine. On the other hand, less nucleophilic amines such as p-nitroaniline do not react at all with dipivaloylketene-dimer **1** under these conditions.

We are currently investigating the reactions of **1** with other nucleophiles, such as alcohols or mercaptanes to get further insights in the reaction mechanism of this unusual transformation (**1** → **2**). In addition this work should eventually provide a practical synthetic route to various functionalized 2,6,9-trioxabicyclo[3.3.1]nona-3,7-dienes.

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REFERENCES AND NOTES

1. Kappe, C. O.; Evans, R. A.; Kennard, C. H. L.; Wentrup, C. *J. Am. Chem. Soc.* **1991**, *113*, 4234-4237.
2. All new compounds gave spectroscopic and analytical data in accordance with the assigned structures. Data for compound **2a**: IR (KBr): ν = 3430 (NH), 3060 (=C-H), 3000-2870 (C-H), 1665,1655sh (C=O), 1600 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.04, 1.14, 1.20, 1.24 (4s, 36H, 4 t-butyl), 4.87 (s, 1H, =CH), 7.06-7.53 (m, 5H, Ph) ppm. ^{13}C-NMR ($CDCl_3$), ring-carbons only: δ = 92.03 (d, $^1J_{CH}$ = 164 Hz, C-8), 97.09 and 99.59 (2 m, C-1 and C-5), 105.52 (s, C-4), 161.74 and 162.13 (2 m, C-3 and C-7), 166.93 (s, CO) ppm.
3. X-ray crystallographic analysis of **2a**: A colorless specimen of size 0.84 x 0.30 x 0.30 mm^3 was investigated at ambient temperature. Crystals are monoclinic, space group $P2_1/c$, Z = 4, δ_c = 1.08 g/cm^3, a = 14.185(21)Å, b = 11.960(18)Å, c = 18.257(31)Å, β = 110.80(10)°, V = 2895.6 Å^3. Cell parameters were obtained by a least squares fit to the diffractometer setting angles of 40 reflections with 2Θ between 8° and 15°. The data collection for two octants of reciprocal space (Mo-K_α radiation, λ = 0.71069 Å, ω-scans with variable speed and $\Delta\omega$ = 1.0°) yielded 7414 reflections with 5° < 2Θ < 55°, 6652 reflections unique, and 2435 with $I/\sigma(I) > 2$. The structure was solved by direct methods, after several refinement cycles with isotropic thermal parameters, an empirical absorption and volume correction was applied. Finally all non-hydrogen atoms were refined with anisotropic thermal parameters, the phenyl group and all methyl groups were treated as rigid fragments. Torsion angles were refined for the bonds to the pivot atoms. Hydrogen-atoms were included in the refinement with isotropic thermal parameters (with the exception of the amide hydrogen). The minimized quantity was $\Sigma(|F_o| - |F_c|)^2$, final R = 0.0619 for 373 parameters and 2435 observations, the final electron difference density map showed features between -0.16 e-/Å^3 and 0.17 e-/Å^3. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ. Any request should be accompanied by the full literature citation for this communication.
4. (a) Gibson, D.; Oldham, C.; Lewis, J.; Lawton, D.; Mason, R.; Robertson, G. B. *Nature (London)* **1965**, *208*, 580-581. (b) Gibson, D.; Lewis, J.; Oldham, C. *J. Chem. Soc. A.* **1967**, 72-77. (c) Mason, R.; Robertson, G. B. *J. Chem. Soc. A* **1969**, 492-497. (d) De Renzi, A.; Panunzi, A.; Paolillo, L.; Vitagliano, A. *J. Organomet. Chem.* **1977**, *124*, 221-228.
5. (a) Arnold, Z.; Budesinsky, M. *J. Org. Chem.*, **1988**, *53*, 5352-5353. (b) Podlaha, J.; Podlahova, J.; Arnold, Z.; Maly, K.; Petricek, V. *Acta Cryst.* **1988**, *C44*, 1966-1968.
6. ^{1}H-NMR spectra of **5** and **6** (200 MHz, $CDCl_3$) exhibit only one set of signals in accordance with the proposed structures, indicating the presence of one single diastereo-isomer.
7. e.g.: N-Benzyl-dipivaloylacetamide, m.p. 130-132 °C; IR (KBr): ν = 3340 (NH), 3000-2880 (CH), 1720 (C=O), 1650 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.18 (s, 18H, 2 t-butyl), 4.39 (d, J = 5.5Hz, 2H, CH_2), 5.72 (s, 1H, CH), 7.12 (br, 1H, NH), 7.18-7.35 (m, 5H, Ph) ppm.

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